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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,602	05/24/2006	Stuart A. Berger	10723-107	7284

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EXAMINER	
WEBB, WALTER E	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
12/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,602	BERGER ET AL.	
	Examiner	Art Unit	
	Walter E. Webb	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,11,20-31,45 and 56* is/are pending in the application.

4a) Of the above claim(s) *1,6-8,11,45 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-31* is/are rejected.

7)☒ Claim(s) *20-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/2006, 2/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 6-8, 11, 20-31, 45 and 56 are pending.

Claims 1, 6-8, 11, 45 and 56 are withdrawn from consideration.

Claims 20-31 are currently under examination.

Election/Restrictions

Applicant's election without traverse of Group II (claims 20-31) in the reply filed on November 2, 2007 is acknowledged.

Claims 1, 6-8, 11, 45 and 56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 2, 2007.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claims 20-31 are objected to because of the following informalities: P-gp is not spelled out. Abbreviations should be spelled out initially to avoid confusion. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating multi-drug resistance with ketotifen in leukemia cells, and the MCF-7 breast cancer cell line, does not reasonably provide enablement for preventing multi-drug resistance or treating cancer in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: The claimed invention is drawn to a method for preventing multi-drug resistance in an animal (claim 20), or in cancer cells (claim 23) with ketotifen and treating cancer with the same (claim 26). However, such a situation is sufficiently unusual. Data would need to be shown in order to establish which specific types of cancer have sensitivity to such a composition and how such cancers could be effectively treated through the administration of the claimed active agent. Because the specification fails to direct the skilled artisan as to which cancers are known to be sensitive to such a composition or how one would even go about determining the subset of cancers that would have been reasonably expected to have such a sensitivity, especially in consideration of the highly complex nature of cancer, the specification, which lacks an objective showing of which cancers could be effectively treated using the

claimed combination of active agents, is viewed as lacking an enabling disclosure of the same. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering the presently claimed active agent, all cancers with any degree of sensitivity whatsoever to such an agent could be treated.

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention of multi-drug resistance or treatment of any cancer, could be effectively achieved by the administration of ketotifen. Based on the state of the art, as discussed below, the artisan would have only accepted that the treatment of multi-drug resistance with a specific cancer type could be achieved with ketotifen, rather than that such an agent could have been used to prevent multi-drug resistance or treat any known cancer.

As set forth in In re Marzocchi et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such

a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling."

Here, the objective truth that cancer of any type may be treated is doubted because, while the state of the art of cancer treatment is well developed with regard to the treatment of specific cancer types (see Rubin et al., "Principles of Cancer Treatment: Management of Cancer Cases." ACP Medicine Online, http://www.medscape.com/viewarticle/534498), the state of the art with regard to treating or preventing cancer in general is grossly underdeveloped.

In this regard, Rubin et al. is cited. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer cell. The Rubin reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer cells for each and every type of cancer (see Treatment, pp 2-3.).

Given that there was not known any specific agent or combination of agents effective to treat all known types of cancer, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved in any cancer type. The artisan would have required sufficient direction as to which specific types of cancer could be effectively treated with the presently claimed combination of active agents and, further, how the artisan could predict what particular types of cancer

would actually show sensitivity to the presently claimed composition such that the artisan would have been imbued with at least a reasonable expectation of success in treating the cancer. Such success would not have been reasonably expected for all cancer types given the highly complex and variable nature of all cancers known in the art and that the treatment of all known cancer types would have been an outcome not reasonably expected by one of ordinary skill in the art. To the artisan, the concept of a single agent, or even a combination of agents, that is effective to treat all known types of cancer would have been unique and, thus, met with a great deal of skepticism.

In light of the state of the art regarding cancer therapy, which is highly complex and highly unpredictable, the present disclosure fails to provide adequate disclosure directing the skilled artisan to the particular types of cancers that may be effectively treated using the claimed active agents.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of human cancer, there is no apparent disclosure to support the contention that the use of the claim specified active agents could actually effectively treat a cancer of any known type by simply administering, by any method, an amount of the claimed active agent, since the present specification fails to enable one of ordinary skill in the art to practice the entirety of the presently claimed invention.

Factor 4: Applicant has merely disclosed that by administering Ketotifen, one may treat cancer of any type or prevent multidrug resistance. Based on the discussion

in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factor 5: The specification at pages 16, 17, 20, 21, and 24-27 provides working examples of in vivo and in vitro data showing increased cytotoxicity of doxorubicin with ketotifen. While the present claims encompass preventing multidrug resistance and treating any cancer, Applicant's data merely establishes dosage dependent lowering of multidrug resistance in MCF-7 and P388 cell lines. No data has been provided, or reasonable scientific basis exists, for treating such results as a prevention of multidrug resistance or treatment for any cancer.

Factor 6: The burden of enabling the treatment of all types of human cancer is much greater than that of enabling the treatment of a specific, discrete group of cancers known to, or with a reasonable basis for concluding that they would, be responsive to such a treatment. Since the present specification would not enable the skilled artisan to treat any type of cancer known in the art or prevent multidrug resistance, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that treatment of cancer of any type (with exception to claim 14) could be achieved with the presently claimed combination of agents. In order to actually achieve such an objective, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant has failed to demonstrate, via direct evidence or sound reasoning, that all types of human cancer could actually be treated with the presently claimed agent, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 20-31 are deemed properly rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20-22 are indefinite because it is not clear what is meant by the phrase "preventing a chemotherapeutic drug subject to multi-drug resistance by P-gp induced cardiac tissue damage in an animal." See line 2-3 of claim 20.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hu et al., (Biochemical Pharmacology 1995) in view of Tamai et al., (Advanced Drug Delivery Reviews 1996).

Applicant invention is drawn to treating multi-drug resistance in an animal or cancer cells by administering ketotifen and a chemotherapeutic drug subject to multi-drug resistance by P-glycoprotein (P-gp), where the chemotherapeutic drug can be anthracyclin or doxorubicin.

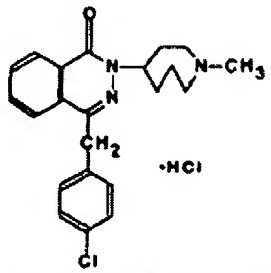
Hu et al., teach that Azelastine and its analogue Flezelatine reverses resistance to doxorubicin in a multi-drug resistance cancer cell line by interfering with P-gp. (See

abstract.) They teach that these compounds possess key features of multi-drug resistant-reversing drugs in that they have an important lipophilicity in relation to the presence of several aromatic rings, and a nitrogen atom ionized to a large extent at neutral pH. (See pg. 170, left column, first full paragraph.)

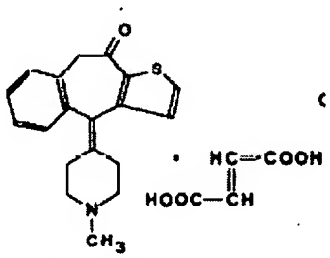
Hu et al. do not teach an *in vivo method*, the use of ketotifen, or where the chemotherapeutic drug can be anthracyclin.

Tamai et al. teach that Azelastine and Ketotifen, both H_1-Antagonists having similar structure, are transported into the brain via the same transport system. (See fig. 3 at pg. 407, and pg. 409, left column, first paragraph.) They also teach that anthracyclin is subject to multi-drug resistance due to P-gp. (See pg. 415, top of right column.)

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to use Ketotifen to treat multi-drug resistance since a compound of similar structure and function was used to treat multi-drug resistance. Ketotifen, shown below with Azelastine, shares the key features of multi-drug resistance-reversing drugs taught in Hu et al. Notice the lipophilicity in relation to the presence of several aromatic rings, and the nitrogen atom that would be ionized at neutral pH.



Azelastine hydrochloride



Ketotifen fumarate

Because Azelastine and Ketotifen possess these similar structural characteristics and are known in the art to have the same utility, and mechanism of transport, the artisan would reasonably conclude that Ketotifen would also serve as mult-drug resistance-reversing drug. "[A] person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1390.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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